

## Recombinant viruses for cancer therapy

Chulpanova D., Solovyeva V., Kitaeva K., Dunham S., Khaiboullina S., Rizvanov A.  
*Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia*

---

### Abstract

© 2018 by the authors. Recombinant viruses are novel therapeutic agents that can be utilized for treatment of various diseases, including cancers. Recombinant viruses can be engineered to express foreign transgenes and have a broad tropism allowing gene expression in a wide range of host cells. They can be selected or designed for specific therapeutic goals; for example, recombinant viruses could be used to stimulate host immune response against tumor-specific antigens and therefore overcome the ability of the tumor to evade the host's immune surveillance. Alternatively, recombinant viruses could express immunomodulatory genes which stimulate an anti-cancer immune response. Oncolytic viruses can replicate specifically in tumor cells and induce toxic effects leading to cell lysis and apoptosis. However, each of these approaches face certain difficulties that must be resolved to achieve maximum therapeutic efficacy. In this review we discuss actively developing approaches for cancer therapy based on recombinant viruses, problems that need to be overcome, and possible prospects for further development of recombinant virus based therapy.

<http://dx.doi.org/10.3390/biomedicines6040094>

---

### Keywords

Cell therapy, Chimeric antigen receptor (CAR) T-cell therapy, Gene therapy, Oncolytic viruses, Recombinant viruses, Virus-based vaccines

### References

- [1] Torre, L.A.; Bray, F.; Siegel, R.L.; Ferlay, J.; Lortet-Tieulent, J.; Jemal, A. Global cancer statistics, 2012. *CA Cancer J. Clin.* 2015, 65, 87-108
- [2] Padma, V.V. An overview of targeted cancer therapy. *BioMedicine* 2015, 5, 19
- [3] Das, S.K.; Menezes, M.E.; Bhatia, S.; Wang, X.Y.; Emdad, L.; Sarkar, D.; Fisher, P.B. Gene therapies for cancer: Strategies, challenges and successes. *J. Cell. Physiol.* 2015, 230, 259-271
- [4] Palucka, K.; Banchereau, J. Dendritic-cell-based therapeutic cancer vaccines. *Immunity* 2013, 39, 38-48
- [5] Wang, M.; Yin, B.; Wang, H.Y.; Wang, R.F. Current advances in T-cell-based cancer immunotherapy. *Immunotherapy* 2014, 6, 1265-1278
- [6] Srivatsan, S.; Patel, J.M.; Bozeman, E.N.; Imasuen, I.E.; He, S.; Daniels, D.; Selvaraj, P. Allogeneic tumor cell vaccines: The promise and limitations in clinical trials. *Hum. Vaccines Immunother.* 2014, 10, 52-63
- [7] Gilazieva, Z.E.; Tazetdinova, L.G.; Arkhipova, S.S.; Solovyeva, V.V.; Rizvanov, A.A. Effect of cisplatin on ultrastructure and viability of adipose-derived mesenchymal stem cells. *BioNanoScience* 2016, 6, 534-539
- [8] Chulpanova, D.S.; Kitaeva, K.V.; Tazetdinova, L.G.; James, V.; Rizvanov, A.A.; Solovyeva, V.V. Application of mesenchymal stem cells for therapeutic agent delivery in anti-tumor treatment. *Front. Pharmacol.* 2018, 9, 259
- [9] Xu, X.J.; Tang, Y.M. Cytokine release syndrome in cancer immunotherapy with chimeric antigen receptor engineered T cells. *Cancer Lett.* 2014, 343, 172-178

- [10] Chulpanova, D.S.; Kitaeva, K.V.; James, V.; Rizvanov, A.A.; Solovyeva, V.V. Therapeutic prospects of extracellular vesicles in cancer treatment. *Front. Immunol.* 2018, 9, 1534
- [11] Gilligan, K.E.; Dwyer, R.M. Engineering exosomes for cancer therapy. *Int. J. Mol. Sci.* 2017, 18, 1122
- [12] Lundstrom, K. Latest development in viral vectors for gene therapy. *Trends Biotechnol.* 2003, 21, 117-122
- [13] Rollier, C.S.; Reyes-Sandoval, A.; Cottingham, M.G.; Ewer, K.; Hill, A.V. Viral vectors as vaccine platforms: Deployment in sight. *Curr. Opin. Immunol.* 2011, 23, 377-382
- [14] Fukuhara, H.; Ino, Y.; Todo, T. Oncolytic virus therapy: A new era of cancer treatment at dawn. *Cancer Sci.* 2016, 107, 1373-1379
- [15] Lizee, G.; Gonzales, M.I.; Topalian, S.L. Lentivirus vector-mediated expression of tumor-associated epitopes by human antigen presenting cells. *Hum. Gene Ther.* 2004, 15, 393-404
- [16] Yang, S.; Tsang, K.Y.; Schlom, J. Induction of higher-avidity human ctls by vector-mediated enhanced costimulation of antigen-presenting cells. *Clin. Cancer Res.* 2005, 11, 5603-5615
- [17] Larocca, C.; Schlom, J. Viral vector-based therapeutic cancer vaccines. *Cancer J.* 2011, 17, 359-371
- [18] Coulie, P.G.; Lehmann, F.; Lethe, B.; Herman, J.; Lurquin, C.; Andrawiss, M.; Boon, T. A mutated intron sequence codes for an antigenic peptide recognized by cytolytic T lymphocytes on a human melanoma. *Proc. Natl. Acad. Sci. USA* 1995, 92, 7976-7980
- [19] El-Sharkawy, A.; Al Zaidan, L.; Malki, A. Epstein-barr virus-associated malignancies: Roles of viral oncoproteins in carcinogenesis. *Front. Oncol.* 2018, 8, 265
- [20] Neek, M.; Tucker, J.A.; Kim, T.I.; Molino, N.M.; Nelson, E.L.; Wang, S.W. Co-delivery of human cancer-testis antigens with adjuvant in protein nanoparticles induces higher cell-mediated immune responses. *Biomaterials* 2018, 156, 194-203
- [21] Jin, S.; Cao, S.; Li, J.; Meng, Q.; Wang, C.; Yao, L.; Lang, Y.; Cao, J.; Shen, J.; Pan, B.; et al. Cancer/testis antigens (CTAs) expression in resected lung cancer. *OncoTargets Ther.* 2018, 11, 4491-4499
- [22] Scanlan, M.J.; Gure, A.O.; Jungbluth, A.A.; Old, L.J.; Chen, Y.T. Cancer/testis antigens: An expanding family of targets for cancer immunotherapy. *Immunol. Rev.* 2002, 188, 22-32
- [23] Chakraborty, M.; Schlom, J.; Hodge, J.W. The combined activation of positive costimulatory signals with modulation of a negative costimulatory signal for the enhancement of vaccine-mediated T-cell responses. *Cancer Immunol. Immunother.* 2007, 56, 1471-1484
- [24] Yu, H.; Zhu, Z.; Chang, J.; Wang, J.; Shen, X. Lentivirus-mediated silencing of myosin VI inhibits proliferation and cell cycle progression in human lung cancer cells. *Chem. Biol. Drug Des.* 2015, 86, 606-613
- [25] Li, L.X.; Zhang, Y.L.; Zhou, L.; Ke, M.L.; Chen, J.M.; Fu, X.; Ye, C.L.; Wu, J.X.; Liu, R.Y.; Huang, W. Antitumor efficacy of a recombinant adenovirus encoding endostatin combined with an E1B55KD-deficient adenovirus in gastric cancer cells. *J. Transl. Med.* 2013, 11, 257
- [26] Vermeij, J.; Zeinoun, Z.; Neyns, B.; Teugels, E.; Bourgain, C.; De Greve, J. Transduction of ovarian cancer cells: A recombinant adeno-associated viral vector compared to an adenoviral vector. *Br. J. Cancer* 2001, 85, 1592-1599
- [27] Parato, K.A.; Breitbach, C.J.; Le Boeuf, F.; Wang, J.; Storbeck, C.; Ilkow, C.; Diallo, J.S.; Falls, T.; Burns, J.; Garcia, V.; et al. The oncolytic poxvirus JX-594 selectively replicates in and destroys cancer cells driven by genetic pathways commonly activated in cancers. *Mol. Ther.* 2012, 20, 749-758
- [28] Goshima, F.; Esaki, S.; Luo, C.; Kamakura, M.; Kimura, H.; Nishiyama, Y. Oncolytic viral therapy with a combination of HF10, a herpes simplex virus type 1 variant and granulocyte-macrophage colony-stimulating factor for murine ovarian cancer. *Int. J. Cancer* 2014, 134, 2865-2877
- [29] Seth, P. Vector-mediated cancer gene therapy: An overview. *Cancer Biol. Ther.* 2005, 4, 512-517
- [30] La Rosa, C.; Longmate, J.; Martinez, J.; Zhou, Q.; Kaltcheva, T.I.; Tsai, W.; Drake, J.; Carroll, M.; Wussow, F.; Chiuppesi, F.; et al. MVA vaccine encoding CMV antigens safely induces durable expansion of CMV-specific T cells in healthy adults. *Blood* 2017, 129, 114-125
- [31] Hanwell, D.G.; McNeil, B.; Visan, L.; Rodrigues, L.; Dunn, P.; Shewen, P.E.; Macallum, G.E.; Turner, P.V.; Vogel, T.U. Murine responses to recombinant MVA versus ALVAC vaccines against tumor-associated antigens, gp100 and 5T4. *J. Immunother.* 2013, 36, 238-247
- [32] Kwilas, A.R.; Ardiani, A.; Dirmeier, U.; Wottawah, C.; Schlom, J.; Hodge, J.W. A poxviral-based cancer vaccine the transcription factor twist inhibits primary tumor growth and metastases in a model of metastatic breast cancer and improves survival in a spontaneous prostate cancer model. *Oncotarget* 2015, 6, 28194-28210
- [33] Acres, B.; Bonnefoy, J.Y. Clinical development of MVA-based therapeutic cancer vaccines. *Expert Rev. Vaccine.* 2008, 7, 889-893
- [34] Amato, R.J.; Shingler, W.; Goonewardena, M.; de Belin, J.; Naylor, S.; Jac, J.; Willis, J.; Saxena, S.; Hernandez-McClain, J.; Harrop, R. Vaccination of renal cell cancer patients with modified vaccinia Ankara delivering the tumor antigen 5T4 (TroVax) alone or administered in combination with interferon-alpha (IFN-alpha): A phase 2 trial. *J. Immunother.* 2009, 32, 765-772

- [35] Rochlitz, C.; Figlin, R.; Squiban, P.; Salzberg, M.; Pless, M.; Herrmann, R.; Tartour, E.; Zhao, Y.; Bizouarne, N.; Baudin, M.; et al. Phase I immunotherapy with a modified vaccinia virus (MVA) expressing human MUC1 as antigen-specific immunotherapy in patients with MUC1-positive advanced cancer. *J. Gene Med.* 2003, 5, 690-699
- [36] Madan, R.A.; Mohebtash, M.; Arlen, P.M.; Vergati, M.; Rauckhorst, M.; Steinberg, S.M.; Tsang, K.Y.; Poole, D.J.; Parnes, H.L.; Wright, J.J.; et al. Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: A phase 1 dose-escalation trial. *Lancet Oncol.* 2012, 13, 501-508
- [37] Scurr, M.; Pembroke, T.; Bloom, A.; Roberts, D.; Thomson, A.; Smart, K.; Bridgeman, H.; Adams, R.; Brewster, A.; Jones, R.; et al. Effect of modified vaccinia Ankara-5T4 and low-dose cyclophosphamide on antitumor immunity in metastatic colorectal cancer: A randomized clinical trial. *JAMA Oncol.* 2017, 3, e172579
- [38] Hui, E.P.; Taylor, G.S.; Jia, H.; Ma, B.B.; Chan, S.L.; Ho, R.; Wong, W.L.; Wilson, S.; Johnson, B.F.; Edwards, C.; et al. Phase I trial of recombinant modified vaccinia ankara encoding epstein-barr viral tumor antigens in nasopharyngeal carcinoma patients. *Cancer Res.* 2013, 73, 1676-1688
- [39] Beatty, G.L.; Gladney, W.L. Immune escape mechanisms as a guide for cancer immunotherapy. *Clin. Cancer Res.* 2015, 21, 687-692
- [40] Arriola, E.; Ottensmeier, C. TG4010: A vaccine with a therapeutic role in cancer. *Immunotherapy* 2016, 8, 511-519
- [41] Oudard, S.; Rixe, O.; Beuselinck, B.; Linassier, C.; Banu, E.; Machiels, J.P.; Baudard, M.; Ringeisen, F.; Velu, T.; Lefrere-Belda, M.A.; et al. A phase II study of the cancer vaccine TG4010 alone and in combination with cytokines in patients with metastatic renal clear-cell carcinoma: Clinical and immunological findings. *Cancer Immunol. Immunother.* 2011, 60, 261-271
- [42] Negrier, S.; Escudier, B.; Lasset, C.; Douillard, J.Y.; Savary, J.; Chevreau, C.; Ravaud, A.; Mercatello, A.; Peny, J.; Mousseau, M.; et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. *N. Engl. J. Med.* 1998, 338, 1272-1278
- [43] Duggan, M.C.; Jochems, C.; Donahue, R.N.; Richards, J.; Karpa, V.; Foust, E.; Paul, B.; Brooks, T.; Tridandapani, S.; Olencki, T.; et al. A phase I study of recombinant (r) vaccinia-CEA(6D)-TRICOM and rFowlpox-CEA(6D)-TRICOM vaccines with GM-CSF and IFN- $\alpha$ -2b in patients with CEA-expressing carcinomas. *Cancer Immunol. Immunother.* 2016, 65, 1353-1364
- [44] Remy-Ziller, C.; Thioudellet, C.; Hortelano, J.; Gantzer, M.; Nourtier, V.; Claudepierre, M.C.; Sansas, B.; Preville, X.; Bendjama, K.; Quemeneur, E.; et al. Sequential administration of MVA-based vaccines and PD-1/PD-L1-blocking antibodies confers measurable benefits on tumor growth and survival: Preclinical studies with MVA- $\beta$ Gal and MVA-MUC1 (TG4010) in a murine tumor model. *Hum. Vaccines Immunother.* 2018, 14, 140-145
- [45] Quoix, E.; Ramlau, R.; Westeel, V.; Papai, Z.; Madroszyk, A.; Riviere, A.; Koralewski, P.; Breton, J.L.; Stoelben, E.; Braun, D.; et al. Therapeutic vaccination with TG4010 and first-line chemotherapy in advanced non-small-cell lung cancer: A controlled phase 2B trial. *Lancet Oncol.* 2011, 12, 1125-1133
- [46] Hillman, G.G.; Reich, L.A.; Rothstein, S.E.; Abernathy, L.M.; Fountain, M.D.; Hankerd, K.; Yunker, C.K.; Rakowski, J.T.; Quemeneur, E.; Slos, P. Radiotherapy and MVA-MUC1-IL-2 vaccine act synergistically for inducing specific immunity to MUC-1 tumor antigen. *J. Immunother. Cancer* 2017, 5, 4
- [47] Hardwick, N.R.; Carroll, M.; Kaltcheva, T.; Qian, D.; Lim, D.; Leong, L.; Chu, P.; Kim, J.; Chao, J.; Fakih, M.; et al. p53MVA therapy in patients with refractory gastrointestinal malignancies elevates p53-specific CD8<sup>+</sup> T-cell responses. *Clin. Cancer Res.* 2014, 20, 4459-4470
- [48] Cawood, R.; Hills, T.; Wong, S.L.; Alamoudi, A.A.; Beadle, S.; Fisher, K.D.; Seymour, L.W. Recombinant viral vaccines for cancer. *Trends Mol. Med.* 2012, 18, 564-574
- [49] Cappuccini, F.; Stribbling, S.; Pollock, E.; Hill, A.V.; Redchenko, I. Immunogenicity and efficacy of the novel cancer vaccine based on simian adenovirus and MVA vectors alone and in combination with PD-1 mAb in a mouse model of prostate cancer. *Cancer Immunol. Immunother.* 2016, 65, 701-713
- [50] Schietinger, A.; Greenberg, P.D. Tolerance and exhaustion: Defining mechanisms of T cell dysfunction. *Trends Immunol.* 2014, 35, 51-60
- [51] Anassi, E.; Ndefo, U.A. Sipuleucel-T (provenge) injection: The first immunotherapy agent (vaccine) for hormone-refractory prostate cancer. *Pharm. Ther.* 2011, 36, 197-202
- [52] Plataniias, L.C. Mechanisms of type-I-and type-II-interferon-mediated signalling. *Nat. Rev. Immunol.* 2005, 5, 375-386
- [53] Liu, B.L.; Robinson, M.; Han, Z.Q.; Branston, R.H.; English, C.; Reay, P.; McGrath, Y.; Thomas, S.K.; Thornton, M.; Bullock, P.; et al. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties. *Gene Ther.* 2003, 10, 292-303
- [54] Twumasi-Boateng, K.; Pettigrew, J.L.; Kwok, Y.Y.E.; Bell, J.C.; Nelson, B.H. Oncolytic viruses as engineering platforms for combination immunotherapy. *Nat. Rev. Cancer* 2018, 18, 419-432
- [55] Mathis, J.M.; Stoff-Khalili, M.A.; Curiel, D.T. Oncolytic adenoviruses-Selective retargeting to tumor cells. *Oncogene* 2005, 24, 7775-7791

- [56] Fu, X.; Tao, L.; Wang, P.Y.; Cripe, T.P.; Zhang, X. Comparison of infectivity and spread between HSV-1 and HSV-2 based oncolytic viruses on tumor cells with different receptor expression profiles. *Oncotarget* 2018, 9, 21348-21358
- [57] Waters, A.M.; Johnston, J.M.; Reddy, A.T.; Fiveash, J.; Madan-Swain, A.; Kachurak, K.; Bag, A.K.; Gillespie, G.Y.; Markert, J.M.; Friedman, G.K. Rationale and design of a phase 1 clinical trial to evaluate HSV G207 alone or with a single radiation dose in children with progressive or recurrent malignant supratentorial brain tumors. *Hum. Gene Ther. Clin. Dev.* 2017, 28, 7-16
- [58] Todo, T.; Martuza, R.L.; Rabkin, S.D.; Johnson, P.A. Oncolytic herpes simplex virus vector with enhanced mhc class i presentation and tumor cell killing. *Proc. Natl. Acad. Sci. USA* 2001, 98, 6396-6401
- [59] Breitbach, C.J.; Moon, A.; Burke, J.; Hwang, T.H.; Kirn, D.H. A phase 2, open-label, randomized study of Pexa-Vec (JX-594) administered by intratumoral injection in patients with unresectable primary hepatocellular carcinoma. *Gene Ther. Solid Cancers* 2015, 1317, 343-357
- [60] Ranki, T.; Pesonen, S.; Hemminki, A.; Partanen, K.; Kairemo, K.; Alanko, T.; Lundin, J.; Linder, N.; Turkki, R.; Ristimäki, A.; et al. Phase I study with ONCOS-102 for the treatment of solid tumors-An evaluation of clinical response and exploratory analyses of immune markers. *J. Immunother. Cancer* 2016, 4, 17
- [61] Nokisalmi, P.; Pesonen, S.; Escutenaire, S.; Sarkioja, M.; Raki, M.; Cerullo, V.; Laasonen, L.; Alemany, R.; Rojas, J.; Cascallo, M.; et al. Oncolytic adenovirus ICOVIR-7 in patients with advanced and refractory solid tumors. *Clin. Cancer Res.* 2010, 16, 3035-3043
- [62] Wang, J.N.; Hu, P.; Zeng, M.S.; Liu, R.B. Anti-tumor effect of oncolytic herpes simplex virus G47delta on human nasopharyngeal carcinoma. *Chin. J. Cancer* 2011, 30, 831-841
- [63] Wang, J.; Xu, L.; Zeng, W.; Hu, P.; Zeng, M.; Rabkin, S.D.; Liu, R. Treatment of human hepatocellular carcinoma by the oncolytic herpes simplex virus G47delta. *Cancer Cell Int.* 2014, 14, 83
- [64] Nakatake, R.; Kaibori, M.; Nakamura, Y.; Tanaka, Y.; Matsushima, H.; Okumura, T.; Murakami, T.; Ino, Y.; Todo, T.; Kon, M. Third-generation oncolytic herpes simplex virus inhibits the growth of liver tumors in mice. *Cancer Sci.* 2018, 109, 600-610
- [65] Hwang, T.H.; Moon, A.; Burke, J.; Ribas, A.; Stephenson, J.; Breitbach, C.J.; Daneshmand, M.; De Silva, N.; Parato, K.; Diallo, J.S.; et al. A mechanistic proof-of-concept clinical trial with JX-594, a targeted multi-mechanistic oncolytic poxvirus, in patients with metastatic melanoma. *Mol. Ther.* 2011, 19, 1913-1922
- [66] Andtbacka, R.H.; Kaufman, H.L.; Collichio, F.; Amatruda, T.; Senzer, N.; Chesney, J.; Delman, K.A.; Spitler, L.E.; Puzanov, I.; Agarwala, S.S.; et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J. Clin. Oncol.* 2015, 33, 2780-2788
- [67] Hernandez, C.; Huebener, P.; Schwabe, R.F. Damage-associated molecular patterns in cancer: A double-edged sword. *Oncogene* 2016, 35, 5931-5941
- [68] Prestwich, R.J.; Errington, F.; Diaz, R.M.; Pandha, H.S.; Harrington, K.J.; Melcher, A.A.; Vile, R.G. The case of oncolytic viruses versus the immune system: Waiting on the judgment of solomon. *Hum. Gene Ther.* 2009, 20, 1119-1132
- [69] Garg, A.D.; Martin, S.; Golab, J.; Agostinis, P. Danger signalling during cancer cell death: Origins, plasticity and regulation. *Cell Death Differ.* 2014, 21, 26-38
- [70] Hobohm, U.; Stanford, J.L.; Grange, J.M. Pathogen-associated molecular pattern in cancer immunotherapy. *Crit. Rev. Immunol.* 2008, 28, 95-107
- [71] Kaufman, H.L.; Kim, D.W.; DeRaffele, G.; Mitcham, J.; Coffin, R.S.; Kim-Schulze, S. Local and distant immunity induced by intralesional vaccination with an oncolytic herpes virus encoding GM-CSF in patients with stage IIIC and IV melanoma. *Ann. Surg. Oncol.* 2010, 17, 718-730
- [72] Breitbach, C.J.; Arulanandam, R.; De Silva, N.; Thorne, S.H.; Patt, R.; Daneshmand, M.; Moon, A.; Ilkow, C.; Burke, J.; Hwang, T.H.; et al. Oncolytic vaccinia virus disrupts tumor-associated vasculature in humans. *Cancer Res.* 2013, 73, 1265-1275
- [73] Dispenzieri, A.; Tong, C.; LaPlant, B.; Lacy, M.Q.; Laumann, K.; Dingli, D.; Zhou, Y.; Federspiel, M.J.; Gertz, M.A.; Hayman, S.; et al. Phase I trial of systemic administration of edmonston strain of measles virus genetically engineered to express the sodium iodide symporter in patients with recurrent or refractory multiple myeloma. *Leukemia* 2017, 31, 2791-2798
- [74] Ong, H.T.; Federspiel, M.J.; Guo, C.M.; Ooi, L.L.; Russell, S.J.; Peng, K.W.; Hui, K.M. Systemically delivered measles virus-infected mesenchymal stem cells can evade host immunity to inhibit liver cancer growth. *J. Hepatol.* 2013, 59, 999-1006
- [75] Heo, J.; Reid, T.; Ruo, L.; Breitbach, C.J.; Rose, S.; Bloomston, M.; Cho, M.; Lim, H.Y.; Chung, H.C.; Kim, C.W.; et al. Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer. *Nat. Med.* 2013, 19, 329-336
- [76] Chesney, J.; Puzanov, I.; Collichio, F.; Singh, P.; Milhem, M.M.; Glaspy, J.; Hamid, O.; Ross, M.; Friedlander, P.; Garbe, C.; et al. Randomized, open-label phase II study evaluating the efficacy and safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in patients with advanced, unresectable melanoma. *J. Clin. Oncol.* 2018, 36, 1658-1667

- [77] Carew, J.S.; Espitia, C.M.; Zhao, W.; Kelly, K.R.; Coffey, M.; Freeman, J.W.; Nawrocki, S.T. Reolysin is a novel reovirus-based agent that induces endoplasmic reticular stress-mediated apoptosis in pancreatic cancer. *Cell Death Dis.* 2013, 4, e728
- [78] Cohn, D.E.; Sill, M.W.; Walker, J.L.; O'Malley, D.; Nagel, C.I.; Rutledge, T.L.; Bradley, W.; Richardson, D.L.; Moxley, K.M.; Aghajanian, C. Randomized phase IIB evaluation of weekly paclitaxel versus weekly paclitaxel with oncolytic reovirus (Reolysin®) in recurrent ovarian, tubal, or peritoneal cancer: An nrg oncology/gynecologic oncology group study. *Gynecol. Oncol.* 2017, 146, 477-483
- [79] Noonan, A.M.; Farren, M.R.; Geyer, S.M.; Huang, Y.; Tahiri, S.; Ahn, D.; Mikhail, S.; Ciombor, K.K.; Pant, S.; Aparo, S.; et al. Randomized phase 2 trial of the oncolytic virus pelareorep (reolysin) in upfront treatment of metastatic pancreatic adenocarcinoma. *Mol. Ther.* 2016, 24, 1150-1158
- [80] Villalona-Calero, M.A.; Lam, E.; Otterson, G.A.; Zhao, W.; Timmons, M.; Subramaniam, D.; Hade, E.M.; Gill, G.M.; Coffey, M.; Selvaggi, G.; et al. Oncolytic reovirus in combination with chemotherapy in metastatic or recurrent non-small cell lung cancer patients with kras-activated tumors. *Cancer* 2016, 122, 875-883
- [81] Rossowska, J.; Anger, N.; Szczygiel, A.; Mierzejewska, J.; Pajtasz-Piasecka, E. Intratumoral lentivector-mediated TGF- $\beta$ 1 gene downregulation as a potent strategy for enhancing the antitumor effect of therapy composed of cyclophosphamide and dendritic cells. *Front. Immunol.* 2017, 8, 713
- [82] Jiang, J.; Zhang, Y.; Peng, K.; Wang, Q.; Hong, X.; Li, H.; Fan, G.; Zhang, Z.; Gong, T.; Sun, X. Combined delivery of a TGF- $\beta$  inhibitor and an adenoviral vector expressing interleukin-12 potentiates cancer immunotherapy. *Acta Biomater.* 2017, 61, 114-123
- [83] Wang, H.; Ji, X.; Liu, X.; Yao, R.; Chi, J.; Liu, S.; Wang, Y.; Cao, W.; Zhou, Q. Lentivirus-mediated inhibition of USP39 suppresses the growth of breast cancer cells in vitro. *Oncol. Rep.* 2013, 30, 2871-2877
- [84] Li, L.; Cao, J.; Liu, L.; Zhu, Z.A.; Wu, K.J.; Fei, S.J. Lentivirus-mediated gene transfer of human sTRAIL induced apoptosis in SGC-7901 cells. *Sichuan Da Xue Xue Bao Yi Xue Ban* 2013, 44, 348-351. (In Chinese)
- [85] Ru, Q.; Li, W.; Wang, X.; Zhang, S.; Chen, L.; Zhang, Y.; Ge, Y.; Zu, Y.; Liu, Y.; Zheng, D. Preclinical study of rAAV2-sTRAIL: Pharmaceutical efficacy, biodistribution and safety in animals. *Cancer Gene Ther.* 2017, 24, 251-258
- [86] Ma, H.; Liu, Y.; Liu, S.; Xu, R.; Zheng, D. Oral adeno-associated virus-sTRAIL gene therapy suppresses human hepatocellular carcinoma growth in mice. *Hepatology* 2005, 42, 1355-1363
- [87] Nan, Y.; Guo, L.; Song, Y.; Wang, L.; Yu, K.; Huang, Q.; Zhong, Y. Combinatorial therapy with adenoviral-mediated PTEN and a PI3K inhibitor suppresses malignant glioma cell growth in vitro and in vivo by regulating the PI3K/AKT signaling pathway. *J. Cancer Res. Clin. Oncol.* 2017, 143, 1477-1487
- [88] Mori, A.; Watanabe, M.; Sadahira, T.; Kobayashi, Y.; Ariyoshi, Y.; Ueki, H.; Wada, K.; Ochiai, K.; Li, S.A.; Nasu, Y. The downregulation of the expression of CD147 by tumor suppressor REIC/Dkk-3, and its implication in human prostate cancer cell growth inhibition. *Acta Med. Okayama* 2017, 71, 135-142